

Supplementary References

- S1. Kirschner, D.E., and Blaser, M.J. 1995. The dynamics of *Helicobacter pylori* infection of the human stomach. *J. Theor. Biol.* **176**:281–290.
- S2. VanderEnde, A., et al. 1996. Heterogeneous *Helicobacter pylori* isolates from members of a family with a history of peptic ulcer disease. *Gastroenterology*. **111**:638–647.
- S3. Israel, D.A., et al. 2001. *Helicobacter pylori* genetic diversity within the gastric niche of a single human host. *Proc. Natl. Acad. Sci. U. S. A.* **98**:14625–14630.
- S4. Go, M.F., Kapur, V., Graham, D.Y., and Musser, J.M. Population genetic analysis of *Helicobacter pylori* by multilocus enzyme electrophoresis: extensive allelic diversity and recombinational population structure. *J. Bacteriol.* **178**:3934–3938.
- S5. Rosche, W.A., and Foster, P.L. 1999. The role of transient hypermutators in adaptive mutation in *Escherichia coli*. *Proc. Natl. Acad. Sci. U. S. A.* **96**:6862–6867.
- S6. Israel, D., Lou, A., and Blaser, M.J. 2000. Characteristics of *Helicobacter pylori* natural transformation. *FEMS Microbiol. Lett.* **186**:275–280.
- S7. Nedenskov, I., Sorensen, P., Bukkolom, G., and Bovre, K. 1990. Natural competence for genetic transformation in *Campylobacter pylori*. *J. Infect. Dis.* **161**:365–366.
- S8. Wang, Y., and Taylor, D.E. 1990. Natural transformation in Campylobacter species. *J. Bacteriol.* **172**:949–955.
- S9. Appelmelk, B.J., et al. 2000. Phase variation in H type I and Lewis O epitopes of *Helicobacter pylori* lipopolysaccharide. *Infect. Immun.* **68**:5928–5932.
- S10. Aras, R.A., Small, A.J., Ando, T., and Blaser, M.J. 2002. *Helicobacter pylori* interstrain restriction-modification diversity prevents genome subversion by chromosomal DNA from competing strains. *Nucleic Acids Res.* **30**:5391–5397.
- S11. Takata, T., et al. 2002. Phenotypic and genotypic variation in methylases involved in Type II restriction-modification systems in *Helicobacter pylori*. *Nucleic Acids Res.* **30**:2444–2452.
- S12. Ando, T., et al. 2000. Restriction-modification system differences in *Helicobacter pylori* are a barrier to interstrain plasmid transfer. *Mol. Microbiol.* **7**:1052–1065.
- S13. Mahdavi, J., et al. 2002. *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. *Science*. **297**:573–578.
- S14. Figueiredo, C., et al. 2002. *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J. Natl. Cancer Inst.* **94**:1680–1687.
- S15. Tummuru, M.K.R., Cover, T.L., and Blaser, M.J. 1993. Cloning and expression of a high molecular weight major antigen of *Helicobacter pylori*: evidence of linkage to cytotoxin production. *Infect. Immun.* **61**:1799–1809.
- S16. Covacci, A., et al. 1993. Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. *Proc. Natl. Acad. Sci. U. S. A.* **90**:5791–5795.
- S17. Censini, S., et al. 1996. *cag*, a pathogenicity island of *Helicobacter pylori* encodes type I-specific and disease-associated virulence factors. *Proc. Natl. Acad. Sci. U. S. A.* **93**:14648–14653.
- S18. Akopyanz, N.S., et al. 1998. Analyses of the *cag* pathogenicity island of *Helicobacter pylori*. *Mol. Microbiol.* **28**:37–53.
- S19. Sozzi, M., Crosarri, M., Kim, S.-K., Romero, J., and Blaser, M.J. 2001. Heterogeneity of *Helicobacter pylori* *cag* genotypes in experimentally infected mice. *FEMS Microbiol. Lett.* **203**:109–114.
- S20. Ko, J.S., and Seo, J.K. 2002. *cag* pathogenicity island of *Helicobacter pylori* in Korean children. *Helicobacter*. **7**:232–236.
- S21. Stein, M., Rappuoli, R., and Covacci, A. 2000. Tyrosine phosphorylation of the *Helicobacter pylori* CagA antigen after cag-driven host cell translocation. *Proc. Natl. Acad. Sci. U. S. A.* **97**:1263–1268.
- S22. Asahi, M., et al. 2000. *Helicobacter pylori* CagA protein can be tyrosine phosphorylated in gastric epithelial cells. *J. Exp. Med.* **191**:593–602.
- S23. Backert, S., et al. 2000. Translocation of the *Helicobacter pylori* CagA protein in gastric epithelial cells by a type IV secretion apparatus. *Cell. Microbiol.* **2**:155–164.
- S24. van Doorn, L.J., Figueiredo, C., Sanna, R., Blaser, M.J., and Quint, W.G.V. 1999. Distinct variants of *Helicobacter pylori* *cagA* are associated with *vacA* subtypes. *J. Clin. Microbiol.* **37**:2306–2311.
- S25. Leunk, R.D., Johnson, P.T., David, B.C., Kraft, W.G., and Morgan, D.R. 1988. Cytotoxic activity in broth-culture filtrates of *Campylobacter pylori*. *J. Med. Microbiol.* **26**:93–99.
- S26. Schmitt, W., and Haas, R. 1994. Genetic analysis of the *Helicobacter pylori* vacuolating cytotoxin: structural similarities with the IgA protease type of exported protein. *Mol. Microbiol.* **12**:307–319.
- S27. Phadnis, S.H., Ilver, D., Janzon, L., Normark, S., and Westblom, T.U. 1996. Pathological significance and molecular characterization of the vacuolating toxin gene of *Helicobacter pylori*. *Infect. Immun.* **64**:905–912.
- S28. Telford, J.L., et al. 1994. Gene structure of the *Helicobacter pylori* cytotoxin and evidence of its key role in gastric disease. *J. Exp. Med.* **179**:1653–1658.
- S29. Szabo, I., et al. 1999. Formation of anion-selective channels in the cell plasma membrane by the toxin VacA of *Helicobacter pylori* is required for its biological activity. *EMBO J.* **18**:5517–5527.
- S30. Tombola, F., et al. 1999. *Helicobacter pylori* vacuolating toxin forms anion-selective channels in planar lipid bilayers: possible implications for the mechanism of cellular vacuolation. *Biophys. J.* **76**:1401–1409.
- S31. Scott, D.R., et al. 1998. The role of internal urease in acid resistance of *Helicobacter pylori*. *Gastroenterology*. **114**:58–70.
- S32. Pelicic, V., et al. 1999. *Helicobacter pylori* VacA cytotoxin associated with the bacteria increases epithelial permeability independently of its vacuolating activity. *Microbiology*. **145**:2043–2050.
- S33. Tombola, F., et al. 2001. How the loop and middle regions influence the properties of *Helicobacter pylori* VacA channels. *Biophys. J.* **81**:3204–3215.
- S34. Ricci, V., et al. 1996. Effect of *Helicobacter pylori* on gastric epithelial cell migration and proliferation in vitro: role of VacA and CagA. *Infect. Immun.* **64**:2829–2833.
- S35. Pai, R., Sasaki, E., and Tarnawski, A.S. 2000. *Helicobacter pylori* vacuolating cytotoxin (VacA) alters cytoskeleton-associated proteins and interferes with re-epithelialization of wounded gastric epithelial monolayers. *Cell Biol. Int.* **24**:291–301.
- S36. Eaton, K.A., Cover, T.L., Tummuru, M.K., Blaser, M.J., and Krakowka, S. 1997. Role of vacuolating cytotoxin in gastritis due to *Helicobacter pylori* in gnotobiotic piglets. *Infect. Immun.* **65**:3462–3464.
- S37. Wirth, H.P., Beins, M.H., Yang, M., Tham, K.T., and Blaser, M.J. 1998. Experimental infection of Mongolian gerbils with wild-type and mutant *Helicobacter pylori* strains. *Infect. Immun.* **66**:4856–4866.
- S38. Salama, N.R., Otto, G., Tompkins, L., and Falkow, S. 2001. Vacuolating cytotoxin of *Helicobacter pylori* plays a role during colonization in a mouse model of infection. *Infect. Immun.* **69**:730–736.
- S39. Kalia, N., Bardhan, K.D., Atherton, J.C., and Brown, N.J. 2002. Toxigenic *Helicobacter pylori* induces changes in the gastric mucosal microcirculation in rats. *Gut*. **51**:641–647.
- S40. McClain, M.S., et al. 2001. A 12-amino-acid segment, present in type s2 but not type s1 *Helicobacter pylori* VacA proteins, abolishes cytotoxin activity and alters membrane channel formation. *J. Bacteriol.* **183**:6499–6508.
- S41. Atherton, J.C., et al. 2001. Vacuolating cytotoxin. In *Helicobacter pylori: physiology and genetics*. H.L.T. Mobley, G.L. Mendz, and S.L. Hazell, editors. ASM Press, Washington, DC, USA. 97–110.
- S42. van Doorn, L.J., et al. 1998. Expanding allelic diversity of *Helicobacter pylori* vacA. *J. Clin. Microbiol.* **36**:2597–2603.
- S43. Pagliaccia, C., et al. 1998. The m2 form of the *Helicobacter pylori* cytotoxin has cell type-specific vacuolating activity. *Proc. Natl. Acad. Sci. U. S. A.* **95**:10212–10217.
- S44. Figueiredo, C., et al. 2001. *Helicobacter pylori* genotypes are associated with clinical outcome in Portuguese patients and show a high prevalence of infections with multiple strains. *Scand. J. Gastroenterol.* **36**:128–135.
- S45. Tummuru, M.K.R., Cover, T.L., and Blaser, M.J. 1994. Mutation of the cytotoxin-associated *cagA* gene does not affect the vacuolating cytotoxin activity of *Helicobacter pylori*. *Infect. Immun.* **62**:2609–2613.
- S46. Sharma, S.A., Tummuru, M.K.R., Miller, G.G., and Blaser, M.J. 1995. Interleukin-8 response of gastric epithelial cell lines to *Helicobacter pylori* stimulation in vitro. *Infect. Immun.* **63**:1681–1687.
- S47. Klein, P.D., et al. 1994. The epidemiology of *Helicobacter pylori* in Peruvian children between 6 and 30 months of age. *Am. J. Gastroenterol.* **89**:2196–2200.
- S48. Jones, D.M., Eldridge, J., Fox, A.J., Sethi, P., and Whorwell, P.J. 1986. Antibody to the gastric campylobacter-like organism ("*Campylobacter pyloridis*"): clinical correlations and distribution in the normal population. *J. Med. Microbiol.* **22**:57–62.
- S49. Isomoto, H., et al. 2000. Expression of nuclear factor kappa B in *Helicobacter pylori*-infected gastric mucosa detected with Soutwestern histochimistry. *Scand. J. Gastroenterol.* **35**:247–254.
- S50. D'Elios, M.M., et al. 1997. T helper 1 effector cells specific for *Helicobacter pylori* in the gastric antrum of patients with peptic ulcer disease. *J. Immunol.* **158**:962–967.
- S51. Morris, A.J., Ali, M.R., Nicholson, G.I., Pérez-Pérez, G.I., and Blaser, M.J. 1991. Long term follow-up of voluntary ingestion of *Helicobacter pylori*. *Ann. Intern. Med.* **114**:662–663.
- S52. Hazell, S.L., Lee, A., Brady, L., and Hennessy, W. 1986. Campylobacter pyloridis and gastritis: association with intercellular spaces and adaptation to an environment of mucus as important factors in colonization of the gastric epithelium. *J. Infect. Dis.* **153**:658–663.
- S53. Perez-Perez, G.I., Dworkin, B.D., Chodos, J.E., and Blaser, M.J. 1988. *Campylobacter pylori* antibodies in humans. *Ann. Intern. Med.* **109**:11–17.
- S54. Hessey, S.J., et al. 1990. Bacterial adhesion and disease activity in Helicobacter associated gastritis. *Gut*. **31**:134–138.
- S55. Takeda, K., Kaisho, T., and Akira, S. 2003. Toll-like receptors. *Annu. Rev. Immunol.* **21**:335–376.
- S56. Gewirtz, A.T., et al. 2003. *Helicobacter pylori* evades toll like receptor 5 in innate immunity. *Gastroenterology*. **4**:A592. (Abstr.)
- S57. Krieg, A.M. 2002. CpG motifs in bacterial DNA and their immune

- effects. *Annu. Rev. Immunol.* **20**:709–760.
- S58.Kirkland, T., Viriyakosol, S., Pérez-Pérez, G.I., and Blaser, M.J. 1997. *Helicobacter pylori* lipopolysaccharide can activate 70Z/3 cells via CD14. *Infect. Immun.* **65**:604–608.
- S59.Muotiala, A., Helander, I.M., Pyhala, L., Kosunen, T.U., and Moran, A.P. 1992. Low biological activity of *Helicobacter pylori* lipopolysaccharide. *Infect. Immun.* **60**:1714–1716.
- S60.Pérez-Pérez, G.I., Shepherd, V.L., Morrow, J.D., and Blaser, M.J. 1995. Activation of human THP-1 and rat bone marrow-derived macrophages by *Helicobacter pylori* lipopolysaccharide. *Infect. Immun.* **63**:1183–1187.
- S61.Ogawa, T., et al. 2003. Endotoxic and immunobiological activities of a chemically synthesized lipid A of *Helicobacter pylori* strain 206-1. *FEMS Immunol. Med. Microbiol.* **36**:1–7.
- S62.Glockner, E., et al. 1998. Proteins encoded by the cag pathogenicity island of *Helicobacter pylori* are required for NF- κ B activation. *Infect. Immun.* **66**:2346–2348.
- S63.Vial, J., et al. 2003. Nod 1-dependent proinflammatory responses to *Helicobacter pylori* infection in gastric epithelial cells. *Gastroenterology* **124**:A43. (Abstr.)
- S64.Sharma, S.A., Miller, G.G., Pérez-Pérez, G.I., Gupta, R.S., and Blaser, M.J. 1994. Humoral and cellular immune recognition of *Helicobacter pylori* proteins are not concordant. *Clin. Exp. Immunol.* **97**:126–132.
- S65.Knipp, U., et al. 1996. Partial characterization of a cell proliferation-inhibiting protein produced by *Helicobacter pylori*. *Infect. Immun.* **64**:3491–3496.
- S66.Fan, X.J., et al. 1994. Gastric T lymphocyte responses to *Helicobacter pylori* in patients with H. pylori colonization. *Gut* **35**:1379–1384.
- S67.Heneghan, M.A., McCarthy, C.F., and Moran, A.P. 2000. Relationship of blood group determinants on *Helicobacter pylori* lipopolysaccharide with host Lewis phenotype and inflammatory response. *Infect. Immun.* **68**:937–941.
- S68.Solnick, J., et al. 2003. Modification in the outer membrane proteins of *Helicobacter pylori* during experimental infection of Rhesus monkeys. *Int. J. Med. Microbiol.* **293**(Suppl. 35):113–114.
- S69.Tham, K.T., et al. 2001. *Helicobacter pylori* genotypes, host factors and gastric mucosal histopathology in peptic ulcer disease. *Hum. Pathol.* **32**:264–273.
- S70.Mohammadi, M., et al. 1996. Helicobacter-specific cell-mediated immune responses display a predominant Th1 phenotype and promote a delayed-type hypersensitivity response in the stomachs of mice. *J. Immunol.* **156**:4729–4738.
- S71.Sakagami, T., et al. 1996. Atrophic gastric changes in both *Helicobacter felis* and *Helicobacter pylori* infected mice are host dependent and separate from antral gastritis. *Gut* **39**:639–648.
- S72.Cui, G., et al. 2003. IFN- γ infusion induces gastric atrophy, metaplasia and dysplasia in the absence of *Helicobacter pylori* infection: a role for the immune response in Helicobacter disease. *Gastroenterology* **124**(Suppl. 1):A19. (Abstr.)
- S73.Hruby, Z., et al. 1997. *Helicobacter pylori* in kidney allograft recipients: high prevalence of colonization and low incidence of active inflammatory lesions. *Nephron* **75**:25–29.
- S74.Cappell, M.S., and Garcia, A. 1998. Gastric and duodenal ulcers during pregnancy. *Gastroenterol. Clin. North Am.* **27**:169–195.
- S75.Machado, J.C., et al. 2001. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* **121**:823–829.
- S76.Wu, M.S., et al. 2003. Interleukin-10 genotypes associate with the risk of gastric adenocarcinoma in Taiwanese Chinese. *Int. J. Cancer.* **104**:617–623.
- S77.Beales, I.L., et al. 1997. Effect of transforming growth factor alpha and interleukin-8 on somatostatin release from canine D cells. *Gastroenterology* **112**:136–143.
- S78.Beales, I., et al. 1997. Effect of *Helicobacter pylori* products on gastrin release from cultured canine G cells. *Gastroenterology* **113**: 465–471.
- S79.Prinz, C., Neumayer, N., Mahr, S., Classen, M., and Schepp, W. 1997. Functional impairment of rat enterochromaffin-like cells by interleukin 1 beta. *Gastroenterology* **112**:364–375.
- S80.Odum, L., Petersen, H.D., Andersen, I.B., Hansen, B.F., and Rehfeld, J.F. 1994. Gastrin and somatostatin in *Helicobacter pylori* infected antral mucosa. *Gut* **35**:615–618.
- S81.Tham, T.C.K., et al. 1998. Effect of *Helicobacter pylori* eradication on antral somatostatin cell density in humans. *Eur. J. Gastroenterol. Hepatol.* **10**:289–291.
- S82.Yamamoto, S., et al. 2001. Interactions among gastric somatostatin, interleukin-8, and mucosal inflammation in *Helicobacter pylori*-positive peptic ulcer patients. *Helicobacter* **6**:136–145.
- S83.Graham, D.Y., et al. 1991. *Helicobacter pylori*-associated exaggerated gastrin release in duodenal ulcer patients. The effect of bombesin infusion and urea ingestion. *Gastroenterology* **100**:1571–1575.
- S84.Beardshall, K., et al. 1992. Suppression of *Helicobacter pylori* reduces gastrin releasing peptide stimulated gastrin release in duodenal ulcer patients. *Gut* **33**:601–603.
- S85.Noshiro, M., et al. 2000. Gastric metaplasia in the duodenal bulb shows increased mucosal interleukin-8 activity in *Helicobacter pylori*-positive duodenal ulcer patients. *Scand. J. Gastroenterol.* **35**:482–489.
- S86.Moss, S.F., et al. 1996. Induction of gastric epithelial apoptosis by *Helicobacter pylori*. *Gut* **38**:498–501.
- S87.Fan, X.G., et al. 1996. *Helicobacter pylori* increases proliferation of gastric epithelial cells. *Gut* **38**:19–22.
- S88.Hoshi, T., et al. 1999. Cell damage and proliferation in human gastric mucosa infected by *Helicobacter pylori*: a comparison before and after *H. pylori* eradication in non-atrophic gastritis. *Hum. Pathol.* **30**:1412–1417.
- S89.Correa, P. 1992. Human gastric carcinogenesis: a multistep and multifactorial process. First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* **52**:6735–6740.
- S90.Susser, S. 1962. Civilisation and peptic ulcer. *Lancet* **1**:115–118.
- S91.Warburton-Timms, V.J., et al. 2001. The significance of cagA(+) *Helicobacter pylori* in reflux oesophagitis. *Gut* **49**:341–346.
- S92.Putsep, K., Branden, C.I., Boman, H.G., and Normark, S. 1999. Antibacterial peptide from *H. pylori*. *Nature* **398**:671–672.
- S93.Mattsson, A., Lonroth, H., Quiding-Jarbrink, M., and Svenssonholm, A.M. 1998. Induction of B cell responses in the stomach of *Helicobacter pylori*-infected subjects after oral cholera vaccination. *J. Clin. Invest.* **102**:51–56.
- S94.Breidert, M., et al. 1999. Leptin and its receptor in normal human gastric mucosa and in *Helicobacter pylori*-associated gastritis. *Scand. J. Gastroenterol.* **34**:954–961.
- S95.Mix, H., et al. 2000. Expression of leptin and leptin receptor isoforms in the human stomach. *Gut* **47**:481–486.
- S96.Sobhani, I., et al. 2000. Leptin secretion and leptin receptor in the human stomach. *Gut* **47**:178–183.
- S97.Lewin, M.J., and Bado, A. 2001. Gastric leptin. *Microsc. Res. Tech.* **53**:372–376.
- S98.Konturek, J.W., et al. 2001. Leptin in the control of gastric secretion and gut hormones in humans infected with *Helicobacter pylori*. *Scand. J. Gastroenterol.* **36**:1148–1154.
- S99.Schneider, R., et al. 2001. Leptin mediates a proliferative response in human gastric mucosa cells with functional receptor. *Horm. Metab. Res.* **33**:1–6.
- S100. Wang, G., et al. 2002. Ghrelin: not just another stomach hormone. *Regul. Pept.* **105**:75–81.
- S101. Gokcel, A., et al. 2003. *Helicobacter pylori* has no effect on plasma ghrelin levels. *Eur. J. Endocrinol.* **148**:423–426.
- S102. Banatvala, N., et al. 1993. The cohort effect and *Helicobacter pylori*. *J. Infect. Dis.* **168**:219–221.
- S103. 1994. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7–14 June 1994. *IARC Monogr. Eval. Carcinog. Risks Hum.* **61**:1–241.
- S104. Badawi, A.F., et al. 1995. Role of schistosomiasis in human bladder cancer: evidence of association, aetiological factors, and basic mechanisms of carcinogenesis. *Eur. J. Cancer Prev.* **4**:45–59.
- S105. Parsonnet, J., et al. 1997. Risk for gastric cancer in people with CagA positive or CagA negative *Helicobacter pylori* infection. *Gut* **40**:297–301.
- S106. Touati, E., et al. 2003. Chronic *Helicobacter pylori* infections induce gastric mutations in mice. *Gastroenterology* **124**:1408–1419.
- S107. Hansson, L.E., et al. 1994. Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. *Int. J. Cancer.* **57**:26–31.
- S108. Sipponen, P., and Marshall, B.J. 2000. Gastritis and gastric cancer: western countries. *Gastroenterol. Clin. North Am.* **29**:579–590.
- S109. Lauren, P. 1965. The two histological main types of gastric carcinoma: diffuse and so-called intestinal carcinoma. *Acta Pathol. Microbiol. Scand.* **64**:31–39.
- S110. Clements, W.M., et al. β -Catemin mutation is a frequent cause of Wnt pathway activation in gastric cancer. *Cancer Res.* **62**:3503–3506.
- S111. Smoot, D.T., et al. 1999. Effects of *Helicobacter pylori* on proliferation of gastric epithelial cells in vitro. *Am. J. Gastroenterol.* **94**:1508–1511.
- S112. Sobala, G.M., et al. 1993. Effect of eradication of *Helicobacter pylori* on gastric juice ascorbic acid concentrations. *Gut* **34**:1038–1041.
- S113. Stein, M., et al. 2002. c-Src/Lyn kinases activate *Helicobacter pylori* CagA through tyrosine phosphorylation of the EPIYA motifs. *Mol. Microbiol.* **43**:971–980.